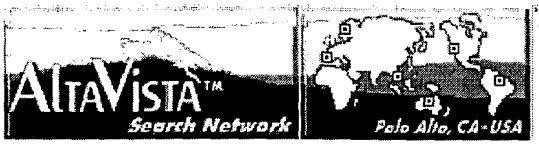

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Abstract Number: 165

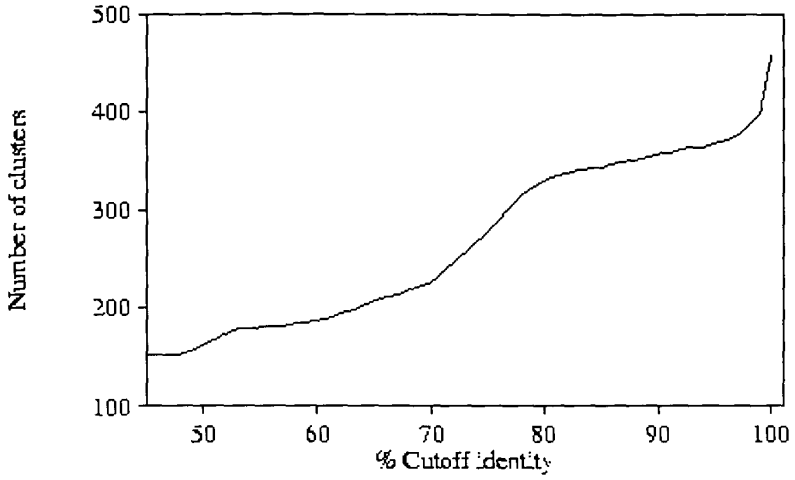
Constructing a set of human genes with low sequence identity

N. Tolstrup, K. Dalsgaard, J. Engelbrecht(*), Soren Brunak

Abstract

A non-redundant set of genes is needed for a wide range of sequence analysis purposes, for example, the estimation of the power of gene finding algorithms. Here we present a new method for redundancy reduction. The redundancy is quantified by similarity measures, but computing distances between genes is non-trivial because the available alignment methods do not in general produce identical results when applied to the same sequences. We extracted 550 human DNA sequences from GenBank, each containing at least one complete human gene with all its exons and introns. All sequences were aligned against each other with three different alignment methods: Global alignment with and without penalty for end gaps ALIGN/ALIGN0 (Myers & Miller 1988), and the FASTA local heuristic alignment method based on hash tables (Pearson 1990). The noise level for each alignment was determined, and thresholds for significant alignments were found. Based on this a distance measure is presented that vanishes for uncorrelated sequences and is non-zero for correlated sequence pairs.

By clustering human DNA sequences using this distance measure a non-redundant data set can be constructed. The figure below shows the number of non-redundant sequences found for clusters with cutoff values ranging from 45 to 100% sequence identity. The choice of the cutoff identity depends on the type of sequence analysis one needs to do. If a small cutoff identity is used, a small set of few, very distant sequences is found, thereby possibly reducing the original data set more than necessary, and thus discarding valuable information. If a very high cutoff is chosen, very close sequence partners are discarded, and many sequences will still be quite similar to each other, thereby possibly biasing the analysis. The correct cutoff is a balance between these two extreme situations. We found 80% to be a sensible choice. A database of human genes with identities below 80% is presented, representing a well defined and truly non-redundant data set.



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- **Keywords:** sequence databases; classification; cluster analysis; Homo Sapiens;, DNA sequences; cutoff values; DNA alignment

Death caspase-1

EVOLUTIONARY HOMOLOGS (part 1/2)

In comparison with other caspase family members, Drosophila caspase-1 is more homologous to CPP-32 and MCH-2alpha than to ICE. It shares 37% sequence identity with both CPP-32 and MCH-2alpha, 29% identity with NEDD-2 (ICH-1), 28% homology with CED-2 and 25% homology with human ICE. This sequence similarity suggests that DCP-1 may be a member of the *ced3*-CPP-32 subfamily of caspases (Song, 1997).

A second Drosophila Caspase has been isolated and termed drICE. drICE is distinct from Death Caspase-1. and exhibits highest homology with the mammalian caspases, Mch2 and CPP32ß. drICE also contains a region in its putative small subunit that corresponds to the P4-specificity loop of CPP32ß. Overexpression of *drICE* sensitizes Drosophila cells to apoptotic stimuli; expression of an N-terminally truncated form of drICE rapidly induces apoptosis in Drosophila cells. Induction of apoptosis by *reaper* overexpression or by cycloheximide or etoposide treatment of Drosophila cells results in proteolytic processing of drICE. drICE is a cysteine protease that cleaves baculovirus p35 and Drosophila lamin DmO in vitro. *drICE* is expressed at all stages of Drosophila development at which programmed cell death can be induced. Levels are highest from 2-6 hours of embryogenesis, lower from 6-12 hours, and still lower after 12 hours of development. These results strongly argue that drICE is an apoptotic caspase that acts downstream of *reaper* (Fraser, 1997).

Properties of caspases

The crystal structure at 2.5 A resolution of a recombinant human ICE-tetrapeptide chloromethylketone complex reveals that the holoenzyme is a homodimer of catalytic domains, each of which contains a p20 and a p10 subunit. The spatial separation of the C-terminus of p20 and the N-terminus of p10 in each domain suggests two alternative pathways of assembly and activation in vivo. Conservation among members of the ICE/CED-3 family of the amino acids that form the active site region of ICE supports the hypothesis that they share functional similarities (Walker, 1994).

In vitro transcribed and translated Ced-3 protein (p56) undergoes rapid processing to smaller fragments. Replacement of the predicted active site cysteine of Ced-3 with serine (C364S) prevents the generation of smaller proteolytic fragments, suggesting that the processing might be an autocatalytic process. Peptide aldehydes with aspartic acid at the P1 position block Ced-3 autocatalysis. Furthermore, the protease inhibition profile of Ced-3 is similar to the profile reported for ICE. These functional data demonstrate that Ced-3 is an Asp-dependent cysteine protease with substrate specificity similar to that of ICE. Aurintricarboxylic acid, an inhibitor of apoptosis in mammalian cells, blocks Ced-3 autocatalytic activity, suggesting that an aurintricarboxylic acid-sensitive Ced-3/ICE-related protease might be involved in the apoptosis pathway(s) in mammalian cells (Hugunin, 1996).

The full-length CED-3 protein undergoes proteolytic activation to generate a CED-3 cysteine protease. CED-3 protease activity is required for killing cells by programmed cell death in *C. elegans*. In its substrate preferences CED-3 is more similar to the mammalian CPP32 protease than to mammalian ICE or NEDD2/ICH-1 protease. These results suggest that different

mammalian CED-3/ICE-like proteases may play distinct roles in mammalian apoptosis and that CPP32 is a candidate for being a mammalian functional equivalent of CED-3 (Xue, 1996).

Members of the caspase family

The *C. elegans* cell death gene ced-3 is most abundant during embryogenesis, the stage during which most programmed cell deaths occur. The predicted CED-3 protein shows similarity to human and murine interleukin-1 beta-converting enzyme and to the product of the mouse nedd-2 gene, which is expressed in the embryonic brain. The sequences of 12 ced-3 mutations as well as the sequences of ced-3 genes from two related nematode species identify sites of potential functional importance. It is proposed that the CED-3 protein acts as a cysteine protease in the initiation of programmed cell death in *C. elegans* and that cysteine proteases also function in programmed cell death in mammals (Yuan, 1993).

Fas/APO-1-mediated apoptosis requires the activation of a class of cysteine proteases, including interleukin-1 beta-converting enzyme (ICE). Triggering of Fas/APO-1 rapidly stimulates the proteolytic activity of ICE. Overexpression of ICE strongly potentiates Fas/APO-1-mediated cell death. Inhibition of ICE activity by protease inhibitors, as well as by transient expression of the pox virus-derived serpin inhibitor CrmA or an antisense ICE construct, substantially suppresses Fas/APO-1-triggered cell death. It is concluded that activation of ICE or an ICE-related protease is a critical event in Fas/APO-1-mediated cell death (Los, 1995).

Nedd2 encodes a protein similar to the mammalian interleukin-1 beta-converting enzyme (ICE) and the product of the *C. elegans* cell death gene ced-3 (CED-3). Overexpression of Nedd2 in cultured fibroblast and neuroblastoma cells results in cell death by apoptosis, which is suppressed by the expression of the human *bcl-2* gene, indicating that Nedd2 is functionally similar to the *ced-3* gene in *C. elegans*. During embryonic development, Nedd2 is highly expressed in several types of mouse tissue undergoing high rates of programmed cell death, such as central nervous system and kidney. This work suggests that Nedd2 is an important component of the mammalian programmed cell death machinery (Kumar, 1994).

The pivotal discovery that Fas-associated death domain protein (FADD) interleukin-1beta-converting enzyme (FLICE)/MACH is recruited to the CD95 signaling complex by virtue of CD95's ability to bind the adapter molecule FADD establishes that this protease has a role in initiating the death pathway. A new member of the caspase family has been cloned, a homologue of FLICE/MACH, and Mch4. Since the overall architecture and function of this molecule is similar to that of FLICE, it has been designated FLICE2. Importantly, the carboxyl-terminal half of the small catalytic subunit that includes amino acids predicted to be involved in substrate binding is distinct. The pro-domain of FLICE2 encodes a functional death effector domain that binds to the corresponding domain in the adapter molecule FADD. Consistent with this finding, FLICE2 is recruited to both the CD95 and p55 tumor necrosis factor receptor signaling complexes in a FADD-dependent manner. A functional role for FLICE2 is suggested by the finding that an active site mutant of FLICE2 inhibits CD95 and tumor necrosis factor receptor-mediated apoptosis. FLICE2 is therefore involved in CD95 and p55 signal transduction (Vincenz, 1997).

A novel apoptotic gene has been cloned from human Jurkat T-lymphocytes. The 32-kDa putative cysteine protease (CPP32) has significant homology to *C. elegans* cell death protein Ced-3, mammalian interleukin-1 beta-converting enzyme (ICE), and the product of the mouse *nedd2*

gene. The CPP32 transcript is highly expressed and most abundant in cell lines of lymphocytic origin. Overexpression of CPP32 or ICE in Sf9 insect cells results in apoptosis. In addition, coexpression of recombinant p20 and p11 derived from the parental full-length CPP32 sequence results in apoptosis in Sf9 cells. Similar to ICE, CPP32 is made of two subunits, p20 and p11, which form the active CPP32 complex. The apoptotic activity of CPP32 and its high expression in lymphocytes suggest that CPP32 is an important mediator of apoptosis in the immune system (Fernandes-Alnemri, 1994).

The enzyme apopain is the protease responsible for the cleavage of poly(ADP-ribose) polymerase, and is necessary for apoptosis. It is composed of two subunits of relative molecular mass (M(r)) 17K and 12K, derived from a common proenzyme identified as CPP32. This proenzyme is related to interleukin-1 beta-converting enzyme (ICE) and CED-3, the product of a gene required for programmed cell death in *C. elegans*. A potent peptide aldehyde inhibitor has been developed and shown to prevent apoptotic events in vitro, suggesting that apopain/CPP32 is important for the initiation of apoptotic cell death (Nicholson, 1995).

The cell surface receptor Fas (Apo-1/CD95) belongs to the tumor necrosis factor/nerve growth factor receptor family; it transmits apoptotic signals by binding to its ligand. Interleukin-1beta-converting enzyme (ICE), which shows substantial homology to the product of *ced-3*, the cell death gene of *C. elegans*, is reported to be involved in Fas-mediated apoptosis. Using two human carcinoma-derived cell lines with undetectable levels of ICE, it was found that an agonistic antihuman Fas antibody induces the activation of CPP32/Yama(-like) proteases that are ICE(-like) protease family members. A tetrapeptide inhibitor of CPP32/Yama protease, DEVD-CHO, inhibits the Fas-mediated activation of the proteases, Fas-mediated apoptosis, and CPP32/Yama(-like) proteolytic activities in vitro. Fas-mediated apoptosis is inhibited by the CPP32/Yama inhibitor DEVD-CHO, but not by the ICE inhibitor YVAD-CHO, suggesting a dominant role for the CPP32/Yama(-like) proteases and not ICE itself in Fas-mediated apoptosis of the human carcinoma cell lines (Hasegawa, 1996).

Upstream regulators of the cell death hierarchy

continued: see Caspase-1: Evolutionary Homologs part 2/2

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The band 4.1 superfamily that includes 81kD ezrin has expanded to include number of new members. An F-actin barbed end capping protein of 82kD from hepat adherens junctions, called radixin, has 75% protein sequence identity to ezrin (1, human heparin-binding protein of 77kD, named moesin, has a protein sequence 74% identical to p81 ezrin (3) and 81% identical to radixin (2). Moesin was found to identical to a human placental p77 protein described earlier (4). All these prote show about 30% sequence identity with the amino-terminal ~260 residues of band 4.1 Other members of this superfamily include talin (5), the product of the neurofibromatosis gene, merlin/schwannomin (6, 7), and two tyrosine protein phosphatases (8, 9).

Ezrin is known to be a phosphoprotein. In A431 cells tyrosine phosphorylat correlates with the EGF-dependent induction of surface structures that contain act ezrin (4). The sites of tyrosine phosphorylation on ezrin have been mapped (10). I recently been shown to become phosphorylated on ser/thr in gastric parietal cells induced to translocate the proton pump to the apical membrane by elevation of cAMP with the coincident appearance of microvilli that contain ezrin (11, 12). Ezrin i relatively specific substrate for calpain I cleavage in parietal cells (13). Ezrin substrate for a tyrosine kinase(s) in T-cells (14). Transfection experiments indi that ezrin has separable domains that associate with the membrane or the cytoskele (15). A previously identified tumor transplantation antigen has been identified as (16).

The distinct contributions of ezrin, radixin and moesin to cellular struct not yet been elucidated. Ezrin and moesin appear to show a very similar localizat cultured cells (17), with both proteins being enriched in surface structures that contain an actin cytoskeleton. Radixin seems to be enriched in adherens junctions focal contacts of cultured cells (1,2); whether it is also present in cell surface structures containing ezrin and moesin is not yet clear (17). Ezrin and moesin ha strikingly different tissue distributions: ezrin is enriched in many epithelial ce where it is generally restricted to the microvilli on the apical aspect of polariz whereas moesin is most abundant in endothelial cells (18). Given the very differe tissue distributions of ezrin and moesin, it is remarkable that both are generally not invariably, found in cultured cells (2,17).

Recent results with cultured cells have revealed that ezrin and moesin can exist as momomers, dimers or heterodimers in vivo or in vitro (19). The homotypic heterotypic association domains are located in the C-terminal halves of the molecu (20).

A summary that includes a discussion of the ezrin, radixin, moesin (ERM) f of proteins has appeared (21).

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